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Second-Line Therapy for Elderly Patients with Non-small Cell Lung Cancer Who Failed Previous Chemotherapy Is as Effective as for Younger Patients

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Introduction: It was found that second-line or thereafter therapies for patients with non-small cell lung cancer (NSCLC) who failed previous chemotherapy yielded a modest survival benefit. However, whether elderly patients (≥70 years) benefit and are as suitable for salvage therapy as nonelderly patients (<70 years) are unknown. Whether epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) is more favorable than chemotherapeutic agents as a salvage therapy agent in elderly patients with NSCLC is also undetermined.

Methods: We retrospectively reviewed and updated the data of our patients with NSCLC who received second-line salvage therapies, classified them into elderly and nonelderly groups, and compared the efficacy, toxicities, and survival of the patients.

Results: Four hundred sixty-one cases were reviewed. The nonelderly group had a similar response rate, control rate, and median survival time than the elderly group ($p = 0.2$, $p = 0.9$, and $p = 0.5$, respectively). The median progression-free time was numerically longer in the elderly than the nonelderly patients ($p = 0.08$). The nonelderly group had statistically insignificantly less hematologic toxicities than the elderly group, but more nausea and vomiting. In addition, the use of EGFR-TKI salvage therapy, compared with salvage chemotherapies in the elderly group, resulted in a similar disease control rate and median survival time and more favorable toxicity profiles.

Conclusions: There were no differences in the efficacy of salvage chemotherapies and EGFR-TKI therapy, in terms of response rate, control rate, and overall survival, in elderly and nonelderly patients, and the therapies had acceptable toxicities. Age itself should not preclude patients with NSCLC from second-line salvage therapy.

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Lung cancer is the leading cause of cancer death in the world.[1] As human longevity increases, there are more and more elderly patients, including lung cancer patients. Lung cancer incidence peaks at about aged 70 to 80 years, and the mortality rate increases with age.[2] The progressive decline of organ functioning, the exhausted functional reserve, and the higher possibility of comorbidities may result in different or higher toxicity profiles and poor survival outcomes in elderly patients with lung cancer, compared with younger patients, when they receive treatment. Elderly patients are more easily frustrated when treatment for lung cancer fails and may refuse further salvage therapy. Thus, the treatments for elderly patients with lung cancer are frequently suboptimal.

With the advances in third-generation chemotherapeutic agents, patients with advanced non-small cell lung cancer (NSCLC) have longer disease control time and survival time, but almost all patients with advanced NSCLC will eventually suffer from disease progression, and die of progression or related complications. There are several chemotherapeutic agents and targeted agents, such as docetaxel and erlotinib, that have been shown to effectively prolong the survival of patients with NSCLC, compared with the best supportive care, and are considered to be effective second-line chemotherapeutic agents.[3–6]

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib or erlotinib, are effective agents used in salvage therapy for NSCLC after patients have failed previous chemotherapy and have different toxicity profiles compared with chemotherapeutic agents used for salvage therapy.[4–6] However, the majority of patients enrolled in these clinical trials using salvage therapy against NSCLC were younger than 70 years. Whether elderly patients are as suitable for salvage therapy as younger patients, and whether salvage targeted therapy is better or more tolerable than salvage chemotherapy in elderly patients are both unknown.

In this study, we retrospectively analyzed the data of our nonelderly (<70 years) and elderly (≥70 years) patients with NSCLC who had failed previous chemotherapy and received

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salvage therapy in our clinical trials previously published in English-language medical journals.[7–15] We wanted to find out whether there existed differences in tolerance and efficacy between young and old patients receiving salvage chemotherapy or salvage targeted therapy with EGFR-TKI.

PATIENTS AND METHODS

We retrospectively reviewed and analyzed our published data of patients with NSCLC who had failed previous chemotherapy and received another chemotherapeutic regimen or gefitinib (an EGFR-TKI) as salvage therapy.[7–15] The data review of the patients who received salvage therapy was approved by the institutional review board of our hospital (VGHIRB No.: 98-03-10A). The patients were classified into a nonelderly group (<70 years) and an elderly group (≥70 years). The treatment response rate, time to disease progression, overall survival time, and toxicity profiles of the two groups were compared. Treatment-related toxicities were recorded, based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.[16] Types of response were assessed with the use of the Response Evaluation Criteria in Solid Tumors.[17] Response rate, time to disease progression, and overall survival time were analyzed with an intention-to-treat principle. Time to disease progression and overall survival time were analyzed using the Kaplan-Meier estimation method and log-rank test. Time to disease progression was calculated from the date of initiation of treatment to the date of disease progression or death. If disease progression had not occurred by the time of this analysis, time to disease progression was considered to have been censored at the time of the last follow-up visit. Survival time was measured from the date of the initiation of treatment to the date of death. Survival time was considered to have been censored at the last follow-up time if death had not occurred. The comparisons of clinical characteristics, response rates, and severity of treatment-related toxicity were performed using the χ^2 analysis.

RESULTS

From September 1998 to October 2005, 461 patients with NSCLC entered nine clinical trials,[7–15] which included treatment with docetaxel alone (weekly or triweekly schedules, $n = 185$)[9,11] or combined with other agents (with ifosfamide, $n = 50$; with gemcitabine, $n = 36$; and with tegafur + uracil, $n = 24$),[9,13,14] gemcitabine alone ($n = 20$) or combined with other agents (with tegafur + uracil, $n = 45$ and with vinorelbine, $n = 17$),[7,8,15] and gefitinib alone ($n = 63$) or with vinorelbine ($n = 21$).[10,12] Their data had been reviewed and updated. Of the 461 patients, 296 (64%) were men and 165 (36%) were women. Among them, 293 patients (64%) were younger than 70 years, and 168 patients (36%) were aged 70 years or older. Among the 168 patients who were aged 70 years or older, 81 patients (48%) were aged 70 to 74 years, 61 patients (36%) were aged 75 to 79 years, 23 patients (14%) were aged 80 to 84 years, and 3 patients (2%) were aged 85 years or older. There was no statistically significant difference in staging and performance status between the nonelderly and elderly groups (Table 1). The objective response rates for salvage therapy, including chemotherapy and/or gefitinib therapy, were 24% in the nonelderly group and 19% in the elderly group ($p = 0.2$). The disease control rates were 68% in the nonelderly patient group and 68% in the elderly patient group ($p = 0.9$). The median progression-free time was 4.1 months (95% confidence interval [CI]: 3.6–4.6 months) in the nonelderly group and 4.4 months (95% CI: 3.6–5.2 months) in the elderly group ($p = 0.08$). The median survival time was 9.3 months (95% CI: 8.0–10.7 months) in the nonelderly group and 8.3 months (95% CI: 6.7–9.9 months) in the elderly group ($p = 0.5$). The 1-year survival rate was 41% in the nonelderly group and 38% in the elderly group (Table 2). When we further divided these patients into subgroups of salvage chemotherapy alone ($n = 377$) or gefitinib treatment alone ($n = 63$), there was still no statistical difference between the nonelderly and elderly groups in terms of response rate, control rate, progression-free survival, overall survival, and 1-year survival (Table 2). More importantly, the elderly patients who received salvage chemotherapy had a response rate, control rate, median time to disease progression, median survival, and 1-year survival rate similar to the elderly patients who received gefitinib salvage therapy (the response rate, control rate, median time to disease progression, median survival, and 1-year survival rate were: 14% versus 30%, $p = 0.1$; 66% versus 70%, $p = 0.8$; 4.2 months versus 4.5 months, $p = 0.2$; 7.6 months versus 6.5 months, $p = 0.8$; and 34% versus 50%, $p = 0.8$, respectively).

Severe treatment-induced hematological toxicities, including grade 3/4 anemia (4% versus 8%, $p = 0.1$), grade 3/4 leukopenia (19% versus 25%, $p = 0.1$), and grade 3/4 neutropenia (25% versus 33%, $p = 0.09$), occurred more frequently in the elderly group. Leukopenic fever occurred at

TABLE 1. Characteristics of All Cases

	N (%)			
	All Cases	**Age <70 yr**	**Age ≥70 yr**	***p***
Patient no.	461 (100)	293 (64)	168 (36)	
Gender				0
Male	296 (64)	156 (53)	140 (83)	
Female	165 (36)	137 (47)	28 (17)	
Mean age (range, yr)	63.5 (23–85)	56.7 (23–69)	75.4 (70–85)	
Performance status				0.6
0	2 (0.4)	2 (0.7)	0	
1	185 (40.1)	116 (39.6)	69 (41.1)	
2	263 (57.0)	166 (56.7)	97 (57.7)	
3	10 (2.2)	8 (2.7)	2 (1.2)	
4	1 (0.2)	1 (0.3)	0	
Stage				0.4
IIIb	42 (9)	29 (10)	13 (8)	
IV	419 (91)	264 (90)	155 (92)	
Histology				0.03
Adenocarcinoma	298 (65)	194 (66)	104 (62)	
Squamous cell	72 (15)	36 (12)	36 (21)	
Other NSCLC	91 (20)	63 (22)	28 (17)	

NSCLC, non-small cell lung cancer.

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TABLE 2. Response Rate, Control Rate, and Survival in All Cases, in the Salvage Chemotherapy Group, and in the Gefitinib Salvage Therapy Group

	All Cases			Salvage Chemotherapy Group			Gefitinib Salvage Group		
	Age <70 yr	Age ≥70 yr	*p*	Age <70 yr	Age ≥70 yr	*p*	Age <70 yr	Age ≥70 yr	*p*
Patient no. (%)	293 (64)	168 (36)		238 (63)	139 (37)		43 (68)	20 (32)	
Chemotherapy cycle, mean ± SD	Nil	Nil	Nil	3.9 ± 1.9	3.6 ± 1.8	0.4	Nil	Nil	Nil
Response rate, %	24	19	0.2	18	14	0.4	49	30	0.2
Control rate, %	68	68	0.9	66	66	0.9	77	70	0.6
Median time to disease progression, mo (95% CI)	4.1 (3.6–4.6)	4.4 (3.6–5.2)	0.08	3.7 (3.1–4.3)	4.2 (3.4–4.9)	0.1	7.5 (3.7–11.3)	4.5 (0–11.7)	0.8
Median survival, mo (95% CI)	9.3 (8.0–10.7)	8.3 (6.7–9.9)	0.5	8.4 (7.0–9.8)	7.6 (6.2–9.0)	0.5	11.0 (5.7–16.2)	9.9 (0–22.1)	0.6
1-yr survival rate, %	41	38		38	34		46	50	

CI, confidence interval.

a slightly higher rate in the elderly group (4% versus 6%, $p = 0.4$). With regard to nonhematologic toxicities, nausea events were significantly more frequent in the nonelderly group (19% versus 8%, $p = 0.01$), but grade 3/4 fatigue was more frequent in the elderly group (4% versus 10%, $p = 0.01$). When considering the patients who received salvage chemotherapy alone ($n = 377$), toxicities occurred more frequently in elderly patients with grade 3/4 anemia (5% versus 9%, $p = 0.1$), grade 3/4 leukopenia (23% versus 30%, $p = 0.1$), grade 3/4 neutropenia (31% versus 40%, $p = 0.08$), leukopenic fever (5.0% versus 7%, $p = 0.4$), and grade 3/4 fatigue (5% versus 12%, $p = 0.01$). Nausea was more frequent in the nonelderly group (23% versus 9%, $p = 0.008$). In contrast, when the patients who received single-agent gefitinib therapy ($n = 63$) were analyzed, all treatment-induced toxicities were found to be similar between the elderly and nonelderly groups. Furthermore, the elderly patients who received salvage chemotherapy alone ($n = 139$) had more frequent grade 3/4 anemia (9% versus 0%, $p = 0.2$), grade 3/4 leukopenia (30% versus 0%, $p = 0.005$), grade 3/4 neutropenia (40% versus 0%, $p = 0.001$), leukopenic fever (7% versus 0%, $p = 0.4$), grade 3/4 fatigue (12% versus 0%, $p = 0.1$), nausea (9% versus 0%, $p = 0.6$), and vomiting (8% versus 0%, $p = 0.6$) than the elderly patient who received gefitinib salvage therapy.

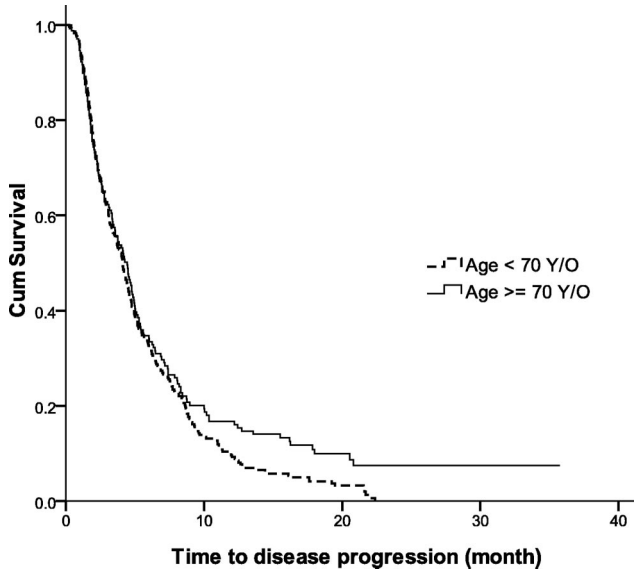

FIGURE 1. Time to disease progression of 293 nonelderly (<70 years) cases and 168 elderly (≥70 years) cases who received salvage chemotherapy or gefitinib salvage therapy. The median time to disease progression were 4.1 months and 4.4 months, respectively ($p = 0.8$).

DISCUSSION

In this study, male patients outnumbered female patients in the elderly group (M/F ratio = 5), whereas they were relatively equal in the nonelderly group (M/F ratio = 1.1). The reason for the male predominance in the elderly group is that these were patients in a veterans' hospital. Adenocarcinoma was the main histologic subtype, and squamous cell carcinoma was relatively more common in the elderly group (nonelderly versus elderly: 12% versus 21%); these results were consistent with our previous study of NSCLC in very young and very old patients.[18]

Another of our previous studies showed that among chemo-naive patients with NSCLC who received first-line chemotherapy, elderly patients had response rates and survival comparable with nonelderly patients.[19] The Ederly Lung Cancer Vinorelbine Italian Study also showed that elderly patients that received first-line chemotherapy had better survival and symptom control than those who received supportive care only.[20] Recently, Crinò et al.[21] reported a randomized phase II study comparing single agent vinorelbine versus gefitinib in chemo-naive elderly NSCLC and the results showed at least in certain patients that EGFR-TKI may produce outcomes similar to single agent chemotherapy in Caucasians, even though the primary end point of superior progression-free survival for gefitinib was not met in this study. However, there is currently no study comparing survival and toxicities with second-line therapy in elderly and nonelderly patients with NSCLC. In this study, there were similar response rates and control rates in the elderly patients and the nonelderly patients. There was no statistically significant difference between the two groups in progression-free time, overall survival time, and 1-year survival rate (Figures 1 and 2). Furthermore, in the subgroup analysis, both salvage

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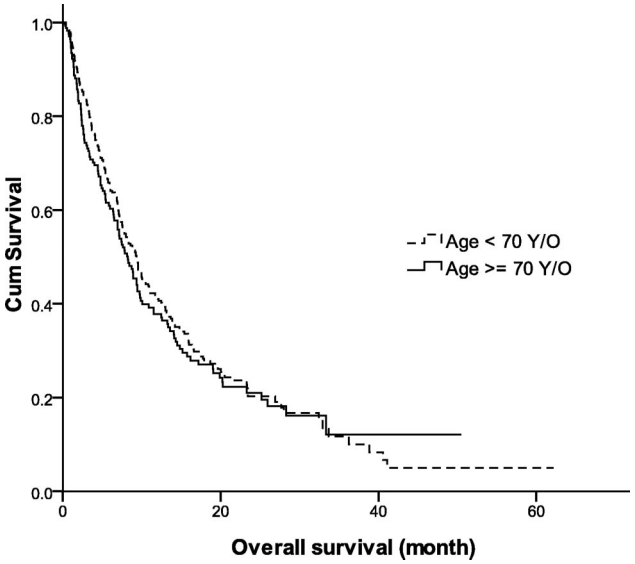

FIGURE 2. Overall survival of 293 nonelderly (<70 years) cases and 168 elderly (≥70 years) cases who received salvage chemotherapy or gefitinib salvage therapy. The median overall survival were 9.3 and 8.3 months, respectively ($p = 0.5$).

chemotherapy and salvage EGFR-TKI therapy showed similar response and survival rates in both age groups. In addition, compared with salvage chemotherapy, salvage EGFR-TKI therapy in the elderly group resulted in similar response rates and 1-year survival rate (chemotherapy versus EGFR-TKI: 34% versus 50%, $p = 0.8$) and had more favorable toxicity profiles. It can be said that old age should not be the factor precluding patients with NSCLC from chemotherapy or EGFR-TKI therapy.

With regard to treatment-related toxicities, both groups had similar hematologic toxicities, but there were more events of fatigue in the elderly patient group and more nausea events in the nonelderly group. Furthermore, in the subgroup analysis, elderly patients who were given salvage chemotherapy had more hematologic toxicities, especially leukopenia and neutropenia, than those who received EGFR-TKI therapy, although leukopenic fever and death due to leukopenic fever were minor and were not statistically significant between the 2 therapies. The elderly patients who underwent salvage chemotherapy had more nausea and fatigue as a result, and those who received EGFR-TKI salvage therapy had more skin rash events. It can be said that salvage chemotherapy and EGFR-TKI therapy result in similar survival in elderly patients with NSCLC, and that EGFR-TKI therapy has more favorable toxicity profiles. This may explain why EGFR-TKI therapy tends to have a numerical longer 1-year survival rate than salvage chemotherapy (chemotherapy versus EGFR-TKI: 34% versus 50%, $p = 0.8$) in elderly patients with NSCLC.

In conclusion, the survival time and hematological toxicities of elderly patients who meet the stringent eligibility for our clinical trials and who received second-line therapy for NSCLC, including both salvage chemotherapy and salvage EGFR-TKI, were comparable with those of nonelderly patients. Thus, age itself should not preclude patients from undergoing second-line therapy for NSCLC. Furthermore, EGFR-TKI therapy had similar response rates and survival time, and more favorable toxicity profiles compared with salvage chemotherapy in elderly patients with NSCLC.

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